



Michael Petrone
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Re: Intranasal Metoclopramide in Diabetic Gastroparesis – Phase III Study Protocol

Dear Dr. Petrone:

As requested during our teleconference of _____ I am attaching two papers that refer to the first of the two pivotal studies for domperidone in diabetic gastroparesis. The second study, a controlled study against metoclopramide has just been published in the Am. J. Gastroenterology

I will be receiving a copy of it within the next few days and I am going to forward it to you via email (as a TIFF file).

My comments remain very much the same as before:

- **Exclusion of non-responders at the end of phase I:** In the domperidone study, ~77% of patients showed improvement and were re-randomized in a treatment and placebo groups in phase II. I think that it will be easy to adopt a similar approach to that of the domperidone study.
- **Careful examination of the underlying statistical assumptions:** Are we really certain that by taking the questionnaires twice will improve the standard deviation by 25% in comparison to the Perkel et al. (1980) study?
- **The validity of using the Perkel et al. (1980) study for the underlying statistical assumptions:** The aforementioned study was mostly in non-diabetic patients (actually, diabetic patients were fully excluded from the statistical calculations). In addition, the enrollment criteria of this study were different; eligible patients had to fail the barium burger test.
- **The structure of the questionnaire:** The questionnaire of our study is identical to that of Perkel et al. (1980) with some minor wording adjustments. The questionnaire of the domperidone study appears to be a simpler version of the Perkel questionnaire. Since the domperidone studies are now published in peer-review publications and address diabetic gastroparesis directly, should

we consider adopting it? Such a step will make our statistical calculations for the appropriate sample size much easier.

Please, forward copies of the papers to the appropriate personnel at GloboMax. I hope that, as soon as they have read these articles, we can reconvene the teleconference on these issues and reach final conclusions regarding the Phase III protocol.

Yours truly,

A handwritten signature in black ink, appearing to read 'A. Retzios', with a long horizontal flourish extending to the right.

Anastassios D. Retzios, Ph.D.
Director of Clinical Operations

Cc: C. Casamento; L. Lehman